The STRIDER trial: one step forward, one step back

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Severe, early-onset fetal growth restriction is characterised by a fetus presenting at a gestational age at the borderline of viability, which is extremely small for gestational age by ultrasonic biometry, and who exhibits other signs of utero-placental insufficiency, such as abnormal patterns of uterine or umbilical blood flow. Following diagnosis, no disease-modifying therapy is available other than medically indicated delivery, which carries a high risk of neonatal death or, if the infant survives, severe neurodisability in later life. Conversely, expectant management carries a substantial risk of intrauterine fetal death. Balancing of these conflicting risks is a day-to-day element of practice in maternal–fetal medicine. Practitioners look to a future of disease-modifying therapies other than delivery.

Unfortunately, the STRIDER trial[1] suggests that one of the promising candidates, sildenafil, is very unlikely to offer hope in this dismal situation. The study was powered to detect a 7-day prolongation in pregnancy. No difference was found in the median randomisation to delivery interval between the placebo group (18 days [IQR 8–28]; p=0·23) and the treatment group (17 days [7–24]), and in reality, the 95% CI (2·7days, 95% CI −1·3 to 6·8; p=0·19) indicates that the best one could expect is a 1·3 day prolongation.

The investigators recruited women with a small for gestational age fetus plus abnormal umbilical artery Doppler flow velocimetry, manifested as absent or reversed end-diastolic flow. Women were eligible from 22 weeks of gestational age onwards. These characteristics identify participants in the STRIDER trial[1] as higher risk than women recruited to the TRUFFLE study,[2] a multicentre, randomised, controlled trial of different forms of fetal assessment in the context of early-onset fetal growth restriction, which reported its primary outcome in 2015. The minimum gestational age for recruitment to the TRUFFLE study[2] was 26 weeks. Moreover, TRUFFLE also included women with forward end-diastolic flow in the umbilical artery, because the inclusion criteria used a pulsatility index more than the 95th percentile. The higher risk nature of the STRIDER group[1] is manifested in higher rates of perinatal death: about 45% of the STRIDER cohort[1] died in utero or in the neonatal period compared with about 8% in the TRUFFLE study.[2]

Participants in the STRIDER trial[1] were randomly assigned to receive sildenafil 25 mg three times a day or a placebo. Subsequent fetal assessment was based on the TRUFFLE protocol.[2] The primary outcome for the trial was delay of delivery but changes in fetal assessment in relation to exposure to the drug or placebo were also analysed, plus a wide range of secondary outcomes. The active treatment was associated with deterioration in indices of fetal wellbeing, specifically in the ductus venosus a-wave (p=0·019). Examination of a range of secondary outcomes showed no better outcomes in the pregnant women treated with sildenafil than those women treated with placebo. In short, the trial was resoundingly negative.

Other candidate disease-modifying treatments are being developed for both early-onset fetal growth restriction and the closely related and commonly co-existing condition of early-onset severe pre-eclampsia. Sildenafil was an exemplar of one approach to identifying novel therapies, namely, the repurposing of drugs licensed for other conditions. This approach involves matching the pathophysiology of severe, early-onset fetal growth restriction to the pharmacology of existing drugs. Other candidates have been ident ified for early-onset fetal growth restriction or pre-eclampsia, or both, including proton-pump inhibitors,[3] metformin,[4] and pravastatin.[5] One positive element to take from the STRIDER trial[1] is that it has taken just 3 years from first recruitment to publication. Moreover, the trial is part of an international network (Global Obstetric Network) and multiple trials have been established internationally using comparable protocols to allow, ultimately, an individual patient meta-analysis. Although it is disappointing that these efforts have yielded a negative result on this occasion, the existence of such a network will be crucial for the evaluation of future candidate treatments.

An alternative approach to repurposing of existing drugs is the development of novel treatments. Target development is also based on our understanding of the disease mechanism. In the case of pre-eclampsia, the available model is that the hypoxic placenta releases the soluble form of the fms-like tyrosine kinase 1 receptor (sFLT1) into the mother's circulation where it binds and inactivates pro-angiogenic growth factors, such as placenta growth factor (PlGF) and vascular endothelial growth factor A (VEGF-A).[6] PlGF and VEGF-A are thought to be essential for the

maintenance of normal endothelial function. Hence, the model links placental dysfunction to maternal endothelial dysfunction, the cardinal feature of pre-eclamspia. Genome-wide association studies and exome sequencing data for pre-eclampsia have identified variants associated with the *FLT1* gene and such observations strongly support a causal role for sFLT1 in the cause of pre-eclampsia.[7,8] This role of elevated sFLT1 raises the possibility of targeted therapies to manipulate the system. One approach is to use therapeutic apheresis to remove sFLT1 from the serum of women with severe, early-onset pre-eclampsia.[9] Another targeted approach to novel therapies, which manipulate angiogenic pathways, is the use of gene therapy, which is being developed for severe, early-onset fetal growth restriction. Adenoviral vectors with the *VEGF* gene are delivered to the uterine artery, inducing both short-term changes in smooth muscle contraction and promoting long-term changes through vascular remodelling.[10] The hope is that correcting maternal underperfusion of the placenta will enhance placental transfer, correcting a key factor in the pathogenesis of the disease.

Although early-onset fetal growth restriction and pre-eclampsia are both rare, the huge lifelong costs of these outcomes justify a substantial focus of resources on research. Doing nothing will result in persistently high rates of stillbirth and cohorts of impaired children, with resulting societal and economic costs. But progress depends on strong candidate therapies and these therapies in turn depend on knowledge of the mechanisms of diseases related to the placenta. Very basic questions remain unanswered. Why do the risks of these conditions vary according to the sex of the fetus? Why is it that placental dysfunction can lead to pre-eclampsia without fetal growth restriction, fetal growth restriction without pre-eclampsia, or the coexistence of both conditions? Hence, basic and translational research are the vital prerequisites to trials such as STRIDER. As the present study shows, however effective the network and trial design, interventional studies will only be as useful as the candidate drugs they evaluate.

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1 Sharp A, Cornforth C, Jackson R, et al. Maternal sildenafil for severe fetal growth restriction (STRIDER): a multicentre, randomised, placebo-controlled, double-blind trial. *Lancet Child Adolesc Health* 2017; published online Dec 6. http://dx.doi.org/10.1016/S2352-4642(17)30173-6.
2 Lees CC, Marlow N, van Wassenaer-Leemhuis A, et al. 2 year neurodevelopmental and intermediate perinatal outcomes in infants with very preterm fetal growth restriction (TRUFFLE): a randomised trial. *Lancet* 2015; **385:** 2162–72.
3 Cluver CA, Walker SP, Mol BW, et al. Double blind, randomised, placebo-controlled trial to evaluate the efficacy of esomeprazole to treat early onset pre-eclampsia (PIE Trial): a study protocol. *BMJ Open* 2015; **5:** e008211.
4 Brownfoot FC, Hastie R, Hannan NJ, et al. Metformin as a prevention and treatment for preeclampsia: effects on soluble fms-like tyrosine kinase 1 and soluble endoglin secretion and endothelial dysfunction. *Am J Obstet Gynecol* 2016; **214:** 356 e1–15.
5 Girardi G. Pravastatin to treat and prevent preeclampsia. Preclinical and clinical studies. *J Reprod Immunol* 2017;**124:** 15–20.
6 Hod T, Cerdeira AS, Karumanchi SA. Molecular mechanisms of preeclampsia. *Cold Spring Harb Perspect Med* 2015; published online Aug 20. DOI:10.1101/cshperspect.a023473.
7 McGinnis R, Steinthorsdottir V, Williams NO, et al. Variants in the fetal genome near FLT1 are associated with risk of preeclampsia. *Nat Genet* 2017; **49:** 1255–60.
8 Lokki AI, Daly E, Triebwasser M, et al. Protective low-frequency variants for preeclampsia in the fms related tyrosine kinase 1 gene in the Finnish population. *Hypertension* 2017; **70:** 365–71.
9 Thadhani R, Hagmann H, Schaarschmidt W, et al. Removal of soluble Fms-like tyrosine kinase-1 by dextran sulfate apheresis in preeclampsia. *J Am Soc Nephrol* 2016; **27:** 903–13.
10 David AL. Maternal uterine artery VEGF gene therapy for treatment of intrauterine growth restriction. *Placenta* 2017; **59** (Suppl 1)**:** S44–50.

Clinical implications of status epilepticus in children

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Status epilepticus (SE) is the most common neurological emergency encountered in childhood; therefore, care providers need to be aware of the acute and chronic implications to accurately counsel patients and their families.[1] The umbrella diagnosis of SE includes numerous subtypes: electrographic SE, convulsive SE, focal SE with impaired consciousness, and absence SE. The most recent guidelines from the International League Against Epilepsy (ILAE) provide two convulsive SE timepoints: the time at which continuous seizure activity requiring the administration of an emergency medication is likely (5 min), and the time at which a continued seizure might lead to permanent neuronal damage (30 min).[2] Unfavorable short-term outcomes after SE, such as in-hospital mortality and